Reviewer's report

Title: LINE-1 methylation is inherited in familial testicular cancer kindreds

Version: 1  Date: 28 December 2009

Reviewer: Apiwat Mutirangura

Reviewer's report:

Mirabello et al presented an interesting and important manuscript. They studied familial testicular cancer kindreds and demonstrated significant correlation between mother and daughter, and father and daughter. Although the correlation between father and son is not significant, there was a strong correlation between affected father and affected son. However, there are several points I would like to suggest that may improve the overall quality of the manuscript.

There may be two important scientific findings here. One is LINE-1 methylation is inherited and the other is LINE-1 methylation is inherited with testicular cancer (epi)genotypes. Moreover, there may be several mechanisms involved in these findings. So I would like to suggest several "Major Compulsory Revisions" as following

1. If number of cases meets enough statistical power, authors should correlate mothers of families with affected fathers with her children, son and daughter. Significant of this result should confirm that LINE-1 methylation is inherited regardless the testicular cancer.

2. It would be interesting to see correlations within each family between unaffected son and unaffected son, daughter and daughter, unaffected son and affected son, daughter and unaffected son, and daughter and affected son. These data may help explain the gender specific of LINE-1 methylation. Note: there are two gender relations with DNA methylation. The first is genomic imprinting and the other may be sex and/or sex chromosomes of the individual.

3. If experimental result of 1 is strong enough, authors may consider changing the topic to clearly emphasize both findings.

4. These findings may be explained by several mechanisms so, in discussion or in introduction, authors should add more references of LINE-1 and LINE-1 methylation characteristics. I find it is crucial to discuss about LINE-1 insertion dimorphisms (LID) [1] and LINE-1 methylation patterns of different loci in normal cells[2]. For example, each family can have number of their ancestor specific LINE-1 insertions. Moreover, these LINE-1s should have methylation levels that are different from means. Therefore, LINE-1 methylation levels can be looked as if they are inherited (instead the result may be due to different number of LINE-1s that posses distinctive methylation levels in different loci). This is important because it may be possible that some LIDs may be linked with testicular cancer susceptible genes.

1. Badge RM, Alisch RS, Moran JV: ATLAS: a system to selectively identify


**Level of interest:** An exceptional article

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'